NDA 203202
Study Endpoint Review:
Orthostatic Hypotension Questionnaire

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Purpose of the Outcome Assessment Review

- To evaluate whether the outcome assessment tool measures what is intended
  - Is the outcome assessment ***well-defined and reliable**** ?
- Important for:
  - Review of a clinical study to determine whether efficacy findings are ***adequate and well-controlled***
  - Analysis and interpretation of study results
  - Description of the effect of treatment in an informative and non-misleading way

*21 CFR 314.126(b)(6)

Proposed Indication Statement

Droxidopa (NORTHERA™) is indicated for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)], dopamine beta hydroxylase (DβH) deficiency and non-diabetic autonomic neuropathy (NDAN). The clinical benefits of NORTHERA™ on ***NOH symptoms and the impact of these symptoms on a patient's ability to perform daily activities that require standing or walking*** *have been demonstrated in placebo-controlled clinical trials.*

Proposed Indication Statement

- Proposed labeling claims include effect of treatment on the following concepts
  - Neurogenic orthostatic hypotension (NOH) symptoms
  - Symptom impact on activities that require standing
  - Symptom impact on activities that require walking
- Is each concept claimed appropriate and relevant?
- Is there evidence that the instrument adequately measures these concepts?

Orthostatic Hypotension Questionnaire (OHQ*)

Domains	NOH symptoms (OHSA)	NOH symptom impacts (OHDAS)
Items	1. Dizziness, lightheadedness 2. Vision 3. Weakness 4. Fatigue 5. Trouble concentrating 6. Head/neck discomfort	1. Standing short time 2. Standing long time 3. Walking short time 4. Walking long time
	OHSA = average of 6 items	OHDAS = average of 4 items

*OHQ summary score= average of the OHSA and the OHDAS scores

Endpoint Model: Study 301

Concept	Endpoint (Mean Change)	Endpoint Position*
NOH symptoms and symptom impacts	OHQ Total	primary
NOH symptom impacts	OHDAS	secondary
NOH symptoms	OHSA	secondary
Impact of NOH symptoms on daily activities that require standing for short time	OHDAS Item 1 score	secondary
Impact of NOH symptoms on daily activities that require walking for short time	OHDAS Item 3 score	secondary
Dizziness/lightheadedness	OHSA Item 1	secondary
Patient global impression of OH severity	Patient CGI-S	secondary
Clinician global impression of OH severity	Clinician CGI-S	secondary
SBP upon orthostatic challenge	SBP upon orthostatic challenge	secondary

* Tested hierarchically

Endpoint Model: Study 302

Concept	Endpoint	Endpoint Position*
Dizziness, lightheadedness	OHSA Item 1	primary
Fatigue	OHSA Item 4	secondary
Weakness	OHSA item 3	secondary
Vision	OHSA item 2	secondary
Concentration	OHSA item 5	secondary
Head/neck discomfort	OHSA Item 6	secondary
Impact of NOH symptoms on daily activities	OHDAS (average items 1-4)	secondary
NOH symptoms	OHSA (average items 1-6)	secondary
Systolic BP during orthostatic challenge	Systolic BP during orthostatic challenge	secondary

* Tested hierarchically

Patient Instructions

- OHSA and OHDAS require patient attribution as part of their instructions to patients
- For example, the OHSA instructs patients:
  - "PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM."
- Patient attribution is infeasible, because multiple other factors may cause similar symptoms or symptom impacts
  - Patients' underlying disease
  - Concomitant medications
  - Other (e.g., family obligations)

I. The Orthostatic Hypotension Symptom Assessment (OHSA)

Please circle the number on the scale that best rates how severe your symptoms from low blood pressure have been ***on the average*** over the past week. Please respond to every symptom. If you do not experience the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

3. Weakness

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

4. Fatigue

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

5. Trouble concentrating

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

6. Head/neck discomfort

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible

II. The Orthostatic Hypotension Daily Activity Scale (OHDAS)

We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by circling the number that best represents how much the activity has been interfered with *on the average* over the past week by the low blood pressure symptoms you experienced.

If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

1. Activities that require standing for a short time												**CANNOT DO FOR OTHER REASONS**
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference** ☐
2. Activities that require standing for a long time												
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference** ☐
3. Activities that require walking for a short time												
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference** ☐
4. Activities that require walking for a long time												
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference** ☐

OHQ Summary Score

- In what setting would it be more meaningful to produce a single overall score representing both NOH symptoms and symptom impacts rather than reporting each domain separately?
- Is OHQ summary score supported by the data?

Content Validity:
Does the instrument measure the concept of interest?

- Qualitative research with patients (patient interviews) answers these questions:
  - What words and phrases do patients use to describe their condition?
  - Do patients understand the instrument items as intended?
  - Is the measure complete and appropriate relative to its use in the clinical trial?
- Content validity hinges on whether the scale is designed in such a way that it captures and quantifies what is important and meaningful with respect to intended disease, population and use

OHSA: Content Validity Concerns (1/2)

- Appropriate scale design?
  - No context provided for rating of symptoms
    - Dizziness or lightheadedness when?
      When lying? Sitting? Standing? Walking?
  - Impossible for patients to tease out how much of their symptoms result from NOH vs. other contributors
  - Patients asked to report their symptoms on *average* over the previous *week*, a complex recall task
    - Simpler to report *worst* symptom on a *daily* basis

OHSA: Content Validity Concerns (2/2)

- Scale completeness?
  - No items included on imbalance or falling, which may reflect the more severe end of the dizziness or dizziness impact spectrum
- Appropriate words/phrases?
  - Fatigue (a general term) is not a word that patients use to describe their condition

Patient Interviews: NOH Symptoms (N=20)

Concept	Cohort 1 (1-5)	Cohort 2 (6-10)	Cohort 3 (11-15)	Cohort 4 (16-20)
Dizziness, lightheadedness	X	X	X	X
Vision Problems		X	X	X
Weakness	X	X	X	X
Tiredness, lack of energy	X	X	X	X
Trouble concentrating		X	X	
Head/neck discomfort		X	X	X
Imbalance	X	X	X	X
Falling	X	X	X	X
Disoriented	X			
Memory problem			X	
Nausea		X		
Pain		X		
Leg pain			X	

OHDAS: Content Validity Concerns

- Appropriate words/phrases?
  - Scale vague and does not give examples of what "long time" and "short time" mean
- Appropriate scale design?
  - Impossible for patients to tease out how much of their symptom impact result from NOH vs. other contributors
- Scale completeness?
  - Omits activities that require positional changes (e.g., sitting to standing)

Construct Validity

- What relationships are expected (i.e., prespecified) among the variables measured and are those hypotheses supported by the data?
- Construct validity cannot be interpreted in the absence of content validity
- We cannot assess construct validity of the OHQ, OHSA, or OHDAS because:
  - Content validity has not been established
  - No evidence provided of prespecified hypotheses about the relationships among variables

OHSA Item 1 (Dizziness/lightheadedness)

- FDA's outcome assessment review concluded that the OHSA-1 (dizziness, lightheadedness) may be described in product labeling if a clinically meaningful difference is observed between treatment groups and the studies are judged to be adequate and well-controlled
- OHSA-1 (dizziness/lightheadedness) reflects one of the core symptoms of NOH

Study 301:

OHSA-1 by Patient Global Impression Severity*

Patient CGI-S	N	Mean OHSA Item #1 Change (SD)	95% CI
Improve>=2 grade	55	-4.29 (2.33)	(-4.92, -3.66)
Improve 1 grade	45	-2.49 (2.18)	(-3.14, -1.83)
No change	45	-1.93 (2.93)	(-2.81, -1.05)
Worse 1 grade	11	0.09 (2.30)	(-1.45, 1.64)
Worse>=2 grade	4	-0.25 (4.27)	(-7.05, 6.55)

* Visit 5 (Final study evaluation) - Visit 2 (Baseline, off drug)

Patient CGI-S: How severe is your orthostatic hypotension (OH) at this time?
1 (normal, no OH); 2 (borderline OH); 3 (mild OH); 4 (moderate OH);
5 (marked OH); 6 (severe OH); 7 (most extremely ill with OH)

Summary

- Content validity is needed for analysis and interpretation of study results and for describing those results in an informative and non-misleading way in product labeling
  - When treatment arm differences are modest, content validity becomes even more critical in evaluating clinical meaningfulness
- FDA's review of the OHQ, OHSA and OHDAS raised concerns regarding their content validity and clinical interpretation
  - None of these scales adequately measures "NOH symptoms" or "impact of NOH symptoms"
- OHSA-1 (dizziness/lightheadedness) reflects one of the core symptoms of NOH
- The treatment effect on OHSA-1 could be represented in labeling as an improvement in "dizziness or lightheadedness" if the changes observed with treatment are judged to be clinically meaningful and the studies are adequate and well-controlled

Droxidopa

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February 23, 2012

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Introduction

- Safety
- Efficacy results
- Durability of efficacy

Safety

Extent of Exposure

ICH Guideline E1

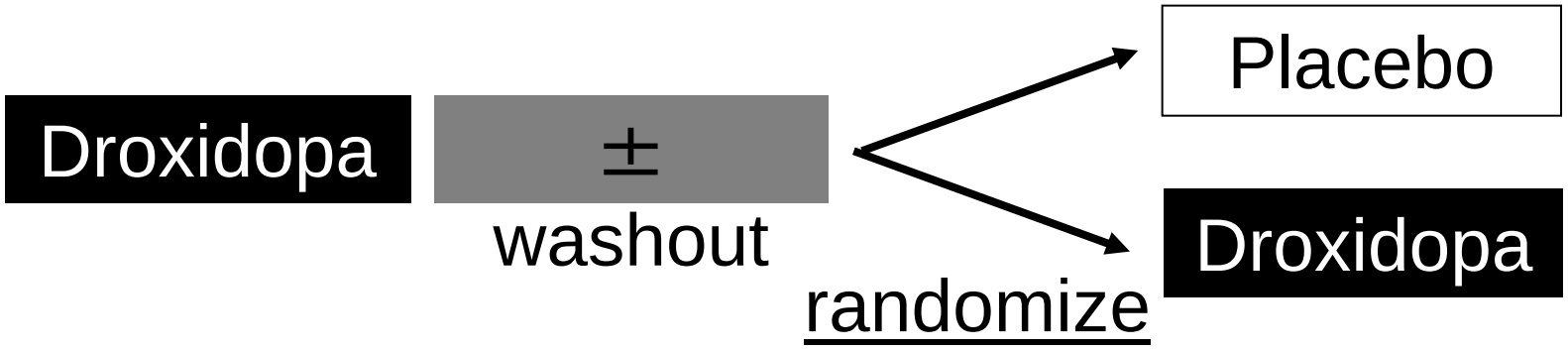
- Population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions
- 1500 total patients: ≥ 300 for 6 months: ≥ 100 for ≥ 1 year - at dosage levels intended for clinical use
- Exceptions: where the intended treatment population is "small".

* Droxidopa was designated as an orphan-drug for the treatment of symptomatic neurogenic orthostatic hypotension – (intended population < 200,000)

Exposure, N

	any	≥6 weeks	≥ 3 months	≥ 6 months	≥1 year	≥ 2 years
Total	535	341	296	220	101	13
highest dose: 600 mg TID	83	81	74	55	28	6
ICH E1	1500			300	100	

Few Controlled Data



- No “pure” placebo patients
- 1 week placebo-controlled data for 301
- 2 week placebo-controlled data for 302 and 303
- Adverse events could be delayed - appear in placebo period as a result of prior exposure
- Could lead to underestimation of adverse event rate
- Long-term exposure – all uncontrolled

Other Limitations of Safety Assessment

- Population studied has high morbidity/mortality; 19 deaths in 222 patient years of exposure in the Phase 3 program and many serious adverse events; difficult to interpret without a control group
- Selected population – patients who couldn't tolerate drug not randomized
  - ~40% of 444 enrolled patients not randomized
  - More than half of these were not randomized because of AEs or BP increase

19 Deaths in Phase 3 Studies

- 18 of 19 deaths - during or after exposure to droxidopa
- 0 deaths on placebo
- 2 deaths in study 302
  - 1 death at screening from unknown cause
  - 1 death 10 days after discontinuation of droxidopa. Patient was on droxidopa for 3 days and experienced severe supine hypertension – on midodrine before death

17 deaths in study 303 and study 304 - during open-label extension period (uncontrolled experience)

Cause of Deaths (1 of 2)

- 9 deaths plausibly related to alpha adrenergic stimulation of norepinephrine
  - 1 stroke
  - 5 sudden deaths
  - 1 severely elevated BP after 2 days of droxidopa – switched to midodrine with sudden death 10 days later
  - 2 patients with myocardial infarction

Cause of Deaths (2 of 2)

- Most other deaths seemed more likely related to underlying conditions, e.g., aspiration pneumonia in 5 patients – a common cause of death in patients with autonomic dysfunction
  - Deaths difficult to interpret without a concurrent placebo group

Non-fatal SAEs of Interest in Phase 3 Studies (1 of 2)

- 11 SAEs plausibly related to alpha adrenergic stimulation of norepinephrine
  - 3 hypertensive crises
  - 1 stroke
  - 1 acute MI
  - 1 CHF
  - 1 atrial fibrillation
  - 2 TIAs
  - 2 unstable angina
- None of these types of SAEs occurred in patients on placebo

Non-fatal SAEs of Interest (2 of 2)

- 2 patients with worsening of their underlying neurological disease
  - difficult to interpret significance in uncontrolled experience

Discontinuations of Interest – from nonserious AEs

83 of 444 (18.5%) patients in studies 301, 302, 303, and 304 discontinued with AEs

2 patients discontinued on placebo in study 302 for AE

- 7 hypertension
- 2 for palpitations
- 1 ventricular extrasystoles
- 1 atrial flutter
- 1 angina
- 1 troponin increase

Other AEs – Difficult to Interpret

- 31 nonserious cases of worsening neurological symptoms, such as tremor
- Headache
- Musculoskeletal complaints
- Dizziness
- Nausea

Deaths in Clinical Trials in Europe/ Japan

- 3 deaths on droxidopa in 3 of several non-Chelsea RCTs – (In DSP-sponsored European studies or in Japan). No deaths on placebo.
  - diabetic with gangrene/sepsis (of 152 patients randomized 2:1, droxidopa to placebo)
  - 42 y/o diabetic with CVA (of 107 patients randomized 1:1, droxidopa to placebo)
  - 43 y/o male with Familial Amyloid Polyneuropathy: multi-organ failure (37 patients randomized to droxidopa/placebo or placebo/droxidopa)
- 16 deaths in open-label trials (3 sudden deaths, 1 myocardial infarction, other mostly pneumonia/ infections)

Neuroleptic Malignant Syndrome

- 28 reports of NMS in patients given droxidopa in post-marketing reports in Japan
- Cases lack sufficient detail for adequate assessment of causality
- > 1/2 cases do not qualify as NMS according to the current diagnostic criteria [Gurrera et al, 2011]
- Most cases include other predisposing factors.
- 64% occurred in summer (heat is associated with NMS)

But, 5 patients not on other drugs known to be associated with NMS; difficult to rule out contributing role of droxidopa in these cases

Summary of Safety

- Overall – a reasonable number of patients exposed – for an orphan indication
- But – several important limitations:
  - Few patients exposed at high dose
  - Placebo-controlled data limited to a short period of time (<= 2 weeks), concerning for a therapy for a chronic disease
  - All patients received droxidopa initially - no “pure” placebo-controlled data
  - Safety population “enriched” for those who could actually tolerate the drug
  - Many background adverse events in this patient population – most adverse events (e.g., deaths) difficult to interpret
- Safety data
  - limited information
  - Somewhat concerning safety signals
  - Difficult to assess causality

Efficacy

design	2-w titration 1-w treatment 2-w random	2-w titration 1-w washout 1-w random	3-m treatment 2-w random
N	101	162	75
Primary Endpoint	Dizziness	OHQ	OHQ
Δ	-0.6	-0.9	-0.3
p-value	0.5	0.003	0.4
Secondary Endpoint	OHQ (Exploratory)	Dizziness	Dizziness
Δ	-1.1	-1.3	-0.4
p-value	0.013	<0.001	0.3

Droxidopa Studies

Study 301

- Statistically persuasive evidence of efficacy
- Well-conducted
- Multi-center
- Consistency across subgroups
- Consistency across endpoints

Studies 302 and 303

- Failed to show benefit on primary efficacy endpoints – or on any symptom endpoints taken individually

Evidence of Effectiveness

- Amendment to the Federal Food, Drug, and Cosmetic Act, 1962:

  "Substantial evidence" > 1 adequate and well controlled trial; interpreted to mean at least 2 adequate and well-controlled trials
- Food and Drug Administration Modernization Act (FDAMA),1997 directed FDA to provide guidance on the circumstances in which <2 trials could meet the definition of "substantial evidence" of effectiveness

Evidence of Effectiveness

1998 FDA Guidance for Industry on when we accept < 2 trials as “substantial evidence” of efficacy :

1. Extrapolation from existing efficacy trials
2. 1 trial + “confirmatory evidence”
3. 1 trial, alone (under certain circumstances)

1998 FDA Guidance: Evidence of Effectiveness Based on <2 Trials (1 of 3)

Evidence of Effectiveness from a Single Study: generally limited to:

- a clinically meaningful benefit on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome
- confirmation in a second trial practically or ethically impossible.

1998 FDA Guidance: Evidence of Effectiveness Based on <2 Trials (2 of 3)

Demonstration of effectiveness by a single study of a new use, with independent substantiation from related study data:

- Different doses, regimens, or dosage forms
- Studies in other phases of the disease
- Studies in other populations
- Studies in combination or as monotherapy
- Studies in a closely related disease
- Studies in less closely related diseases, but where the general purpose of therapy is similar
- Studies of different clinical endpoints
- Pharmacologic/pathophysiologic endpoints

1998 FDA Guidance: Evidence of Effectiveness Based on <2 Trials (2 of 3)

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1998 FDA Guidance: Evidence of Effectiveness Based on <2 Trials (3 of 3)

Pharmacologic/pathophysiologic endpoints

"When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness."

"When the…linkage between (the pharmacologic effect) and the clinical outcome is strong, a single adequate and well-controlled study…can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect."

Pharmacologic/pathophysiologic endpoint

- A rise in standing systolic BP is the pharmacologic/ endpoint of interest - could be used as independent substantiation of efficacy
- Definition of OH: “Reduction of systolic blood pressure of ≥ 20 mm Hg or diastolic blood pressure of ≥ 10 mm Hg within 3 minutes of standing.

  Orthostatic hypotension may be symptomatic or asymptomatic.” (Consensus Committee of the American Autonomic Society and the American Academy of Neurology)
- A treatment for symptomatic orthostatic hypotension needs to affect the blood pressure to a greater or lesser or extent. BP rise is a necessary, not sufficient condition for demonstration of efficacy

Are BP effects persuasive enough to serve as independent substantiation of efficacy?

Efficacy Results – Standing SBP at 3 minutes

STUDY	302	301	303
design	2-w titration 1-w treatment 2-w random	2-w titration 1-w washout 1-w random	3-m treatment 2-w random
N	101	162	75
Standing SBP			
Δ	2.4	7.3	-8.4
p-value	0.7	<0.001	0.3

1998 FDA Guidance: Evidence of Effectiveness Based on <2 Trials (3 of 3)

- BP effect apparent in 301, slight trend in 302
- Paradoxical BP effect (decreases) in 303 – despite trend for symptom benefit
- Data on the pharmacologic effects on BP effect are not "persuasive" and therefore, cannot be construed as "independent substantiation from related study data."

Durability of Effect

STUDY	302	301	303
design	2-w titration 1-w treatment 2-w random	2-w titration 1-w washout 1-w random	3-m treatment 2-w random
N	101	162	75
Primary Endpoint	Dizziness	OHQ	OHQ
Δ	-0.6	-0.9	-0.3
p-value	0.5	0.003	0.4
Secondary Endpoint	OHQ (Exploratory)	Dizziness	Dizziness
Δ	-1.1	-1.3	-0.4
p-value	0.013	<0.001	0.3

Droxidopa Studies

Durability of Effect

- Study 301 showed clinical benefit for only 1 week
- Studies 302 and 303 did not show clinical benefit after 5 weeks or 3 ½ months
- Durability of effect: no regulations; no guidance for this indication
- Drug labeling - requires adequate directions for use
- How to label - chronically or intermittently?
- Approve for only short-term use?
- If labeled for only short-term use, very difficult to restrict more prolonged “off-label” use

Overall Summary

Summary of Safety

- Overall – a reasonable number of patients exposed – for an orphan indication
- But – several important limitations:
  - Few patients exposed at high dose
  - Placebo-controlled data limited to a short period of time (<= 2 weeks), concerning for a therapy for a chronic disease
  - All patients received droxidopa initially - no “pure” placebo-controlled data
  - Safety population “enriched” for those who could actually tolerate the drug
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- Safety data
  - limited information
  - Somewhat concerning safety signals
  - Difficult to assess causality

Summary of Efficacy

- Study 301 shows compelling evidence of efficacy
- Studies 302 and 303 show a trend

*** Only one trial shows efficacy – need more than one trial since there was no effect seen on mortality or irreversible morbidity

Need independent substantiation from a pharmacologic/ pathophysiologic endpoint: persuasive BP findings

BP findings are conclusive in 301, not in 302 or 303; overall, not persuasive

If we accepted efficacy findings as sufficient to support approval, efficacy data limited to only 1 week are problematic; effect may not be durable

Summary

- Clear proof of efficacy and durability lacking
- Safety not well-characterized
- Ideally, we would like more placebo-controlled experience to support efficacy, demonstrated durability and more thoroughly explore safety